THE HORMONES OF THE ANTERIOR PITUITARY

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INTRODUCTION

This Society—"devoted to the promotion of research in science"—may very reasonably ask a speaker to begin his address with a statement of the general or wider meaning of current advances in the field for which he is to speak. Perhaps the usefulness of such a general statement tonight is increased by the circumstance that the present discussion concludes a symposium of 10 lectures on Hormones which this Chapter of Sigma Xi has been resourceful enough to arrange and present within the year. Again, those several earlier and related discussions can very notably reinforce any general statement which might be made concerning advances in the study of the anterior pituitary hormones alone.

Almost too obvious to require mention in such a general statement is the practical certainty that present and future advances in our knowledge of the hormones will make medicine more effective in dealing with at least several diseases and incapacities of man and animals. But rightly notable here, because rather less evident, are two somewhat related things: First, some conditions not classifiable as disease but as subnormal developments of body or mind—such as small stature and some forms of dull mentality—will probably prove more amenable to favorable influence by hormones than from any other therapeutic source. Second, the hormones have already provided the essential basis for an understanding of the cycles and reproductive adjustments peculiar to women, although 15 years ago not one of the several hormones involved in the production of those cycles had been isolated or suitably measured. Another 15 years should add very useful elements of control to our present quite gratifying degree of comprehension of those cyclical adjustments to which one-half of mankind is subjected during much of the span of life.

Further—and this point is of interest to investigators in all branches of science represented in this Society—advancing knowledge of the hormones is enabling us to begin to see and comprehend the mechanisms by which our own complex bodies

maintain their own internal environment at a constant or steady state. Moreover, some of these hormones have even shown themselves to be the means by which certain peculiar aspects of this steady internal state is sometimes greatly upset or changed —likewise to the great advantage of the organism—and all this supplies hitherto missing information on the great problems of biologic organization and adaptation.

Precisely this last-named gain—a gain on a scientific and philosophical question which has long seemed troublesome to some scientific men—has such exceptionally wide application in the sphere of thought that it deserves a central position in this introductory statement. The knotty problems of adaptation and complex animal organization—particularly that of the brain and the regulatory processes of animals—have been thought by some biologists and philosophers to be best accounted for by the assumption of a guiding vitalistic force, a force essentially divorced from matter and akin to the supernatural. As the profound and peculiar regulatory powers of the hormones have become even partly known—particularly since these non-nervous chemical agents have been found to constitute an additional regulatory mechanism affected by both the nervous system and the external environment—the bases of the doctrine of vitalism have been sapped and severely shaken. The newer outlook conforms well with the naturalism so well stated by Darwin in his great study of 1874. And we are encouraged to proceed on the conception that an organism is to be understood, if at all, in terms of its organization, its environment, and its past. Up to now the supernatural has disclosed no sphere or place of its own in organisms.

In calling attention to these broad or general contributions of endocrinological research one should at once note that many other branches of biological or life-science are making similar, perhaps equal or greater, contributions to the present and future well-being of man. Personally I like to think of the sum of all this biological research as affording full justification for the opinion and statement of a great mathematician and chemist who for a generation was president of Harvard University and perhaps America's greatest educational leader. Near the end of his service at Harvard, President Charles W. Elliot said: "The human race has more and greater benefits to expect from the successful cultivation of the sciences which deal with living things than from all the other sciences put together."

Now lest some of my audience at once write me down as an incurable optimist, supremely satisfied with all that is labelled biological, I must add another general statement—and admission. It is this. Though our laboratories of endocrinology and of a dozen other divisions of life-science have all done well within their walls, they have failed in most of the world that lies outside those walls. The thoroughly biological thing that counts is man, the citizen—the walking, sleeping, or perhaps just now, the "sit-down" citizen; and, the future citizens now in public or other schools. These—our present and future citizens—are now left largely untouched by the best products of our biological laboratories. *We learn; but we have established only slender channels to the great stream of the mental life of modern man.* Within the time of men now alive we have learned the broad outlines of man's own nature and man's place in nature; but the citizen is unaware, and the future citizen remains practically untaught. Our very best contributions are to the mental orientation of men—yet any such contribution whatever is contingent upon contact and possession and these are not yet achieved. The laboratories have won only Pyrrhic victories until secondary schools—the only broad path to our people—begin the task of carrying basic biologic truth to our future citizens.

From these very general and introductory reflections concerning endocrinology and its biological settings we may next turn to a consideration of some quite general aspects of present knowledge of "the hormones of the anterior pituitary."

GENERAL CONSIDERATIONS

At this stage of high uncertainty concerning most that pertains to "anterior pituitary hormones" no one would elect to speak or write on that subject. You are asked to understand clearly that I have had no choice; I was drafted, and I am still reluctant. There would be only pleasure in placing before you such observations and measurements concerning some *responses* to pituitary products as have been recently accomplished in our own laboratory; but there is real danger that some opinions on pituitary hormones which I am now forced to put on record will be proved wrong even before the end of the present year. Our actual knowledge of the *hormones*—the elaborated active molecules—of this remarkable gland is so fragmentary that even our first words on the subject must include opinion and specula-

tion. Sensing the harsh and speedy fate that awaits at least some of the speculations which must be set down in the first section of this communication I note that those paragraphs are to be regarded as my own particular view of this subject on this particular day.

To a highly significant degree the hormones of the anterior pituitary have been found to exert their action upon other hormone-producing organs. It now appears that the chief function of the pituitary is to regulate the production of chemical regulators (hormones) in other endocrine glands. The effects of pituitary hormones upon the several glands and processes of the body are both numerous and impressive. Though these effects or responses are as yet imperfectly known, and though several known responses can not yet be definitely assigned to a particular hormone, many responses have been and are now being studied with notable success. As already suggested, however, much less success has attended efforts to learn either the true number or the chemical structure of the pituitary hormones themselves. None of them has been isolated in a satisfactorily pure state; and some of the imperfect isolations accomplished from dead pituitary tissue may represent only fragments of those molecules (hormones) which pituitary cells normally release from their surfaces. These uncertainties as to the number and the chemical structure of A. P. hormones, like the now recognized difficulties encountered in their isolation and purification, are bound up with their probable protein (or polypeptid) nature and with the further complicating circumstance that more than one hormone is produced in the gland; indeed we are faced with a serious probability that more than one hormone is produced by one and the same type of pituitary cell, or even by the same cell.

While speaking of these uncertainties and probabilities we may as well discuss a possible way of regarding the production of a seeming multiplicity of hormones, or of hormone fragments, from two types of secreting cells. Much cytological study of the anterior pituitaries of higher vertebrates indicates the presence there of three special types of cells—chromophobes, eosinophils and basophils—and that only the two last-named types show secretory activity. Again, studies of responses to pituitary hormones or hormone-fragments, and also vague indications obtained from methods of isolating these pituitary products, provide some basis for grouping most or all of the secreted

products into *two* groups. Thus the eosinophil cells would seem to be the source of a prolactin-adrenotropin product; and this substance probably elicits not only the responses already credited to these particular names, but also those responses designated as diabetogenic and ketogenic (and *growth* also in some animals). The basophils would seem to be the source of follicle-stimulating hormone (FSH) and probably for luteinizing and such other gonadotropic hormones or hormone-fragments as may exist (a gonadotropic contribution to the body *growth* of some animals seems also probable). Whether the thyrotropic hormone is of eosinophilic or of basophilic origin now seems only a hazardous guess. But, besides its specific capacity to stimulate the thyroid gland there is also reason to assign growth-promoting capacity (in at least some animals) to this hormone. The conception thus briefly stated requires further immediate comment.

On this view the writer does not find it necessary to allocate a "growth" hormone to either type of cell, since he believes that the unquestionable ability of the pituitary to promote bodily growth really rests upon the aggregate of helpful things contributed by other (perhaps all) pituitary hormones. This view also very definitely assigns to different pituitary hormones unequal growth-promoting rôles in different animal species—e. g., prolactin has been found of chief importance to growth in the pigeon (1, 2); thyrotropic seems of chief importance in the dwarf mouse (3); while no pituitary hormone is required for continued normal growth in some of the lower vertebrates. Again, removal of the pituitary gland (and all of its hormones) in the young rat of 25–35 grams scarcely interferes with its growth until after it reaches a weight of about 60 grams (4); and, the same "growth" extract that will promote growth in normal female rats from the 4th to 10th week of life will or may fail to promote such growth in similar male rats (5). Sex difference as well as species difference is concerned therefore in the growth response of an animal to products of pituitary origin. Of course Evans (6, 7, 8) long ago showed that adult male rats whose growth curves have plateaued can be made to grow with alkaline pituitary extracts. Finally, it is to be noted that in high degree the pituitary hormones (or hormone fragments?) have shown augmentation or synergistic actions upon each other; and one such synergism of the growth response has been observed (3) in the dwarf mouse and another on basal metabolic rate (2)—with prolactin (or prolactin-adrenotropin) and thyrotropic apparently here serving as members of the synergistic pair.

It was indicated above that the product (or products) of eosinophil cells yield many responses—those associated with prolactin, adrenal repair, glycosuria, ketosis, and a rôle in growth. The eosinophilic contribution to the growth response, in most animals, probably exceeds that of the basophilic product. Is more than one eosinophilic product liberated by the living cell? Unless thyrotropic hormone, in addition to prolactin, is of eosinophilic origin I do not think that present evidence compels us to accept even a duality of normally liberated eosinophilic products. Though there is non-negligible evidence for the existence of an adrenotropic hormone, cortical repair—like growth—may yet prove to be a response to other hormones, even involving a synergistic action of these, and not a response to a single entity. Again, it is perhaps conceivable that the structure liberated by the eosinophil cell is a molecule holding prolactin and adrenotropin in combination, and that this molecule is split into parts by the means used for their seeming (partial) isolation from the dead pituitary tissue (see below). Certainly some fragmentary information, particularly that dealing with pituitary influence on carbohydrate metabolism, suggests a close association—perhaps interrelation is the better word—of adrenal maintenance on the one hand with some of the responses to prolactin on the other.

The basophilic product—a gonadotropic complex—is probably responsible for a specific stimulation of *growth* in gametogenic tissue and in interstitial tissues, besides inducing a transformation (luteinization) of granulosa or of thecal cells of female mammals into useful but fated luteal cells (or is the latter process mediated by products originating in adrenals, gonads, etc.?). The number of hormones, or of hormone fragments, involved in regulating these responses is not clear. The status of FSH as a definite normally released product of the pituitary is conceded by all investigators. The almost complete separation of two fractions having gametogenic (FSH) and luteinizing (LH) properties has been reported by Fevold, Hisaw *et al* (9) and Wallen-Lawrence (10). Evans *et al* (11) report still other active fractions; and Smith, Engle and Tyndale (12) report fairly complete separation of one principle (LH) from pregnancy urine and another (FSH) from castrate and menopausal urine.

Since pituitary *hormones*—not *responses* to pituitary products—are the subject of this paper we must further pursue these considerations. Not only may our extraction methods pick up

unfinished hormone fragments from the interior of dead pituitary cells; these methods—in addition to their known capacity to inactivate (more or less rapidly) the true hormones themselves—are perhaps also capable of both physically *separating* and of *chemically changing* two or more of the fragments that should form a molecule of a true hormone. It is improbable, though conceivable, that some apparant synergisms among pituitary products may rest therefore upon the chance given such fragments to recombine (when later put simultaneously in the blood stream) and form more of the true hormone. On *a priori* grounds there is a fair probability that some of these fragments of hormones have physiological activity, but physiological activity that is not identical with that of the entire molecule (hormone) which is normally liberated by the living pituitary cell. If this is true, our pituitary "extracts" contain a greater number of active products than of products to which the name hormone properly applies.

From what has just been stated it is clear that some importance attaches to the fact that certain pituitary hormones have been recovered from the blood. Though present failure to find certain pituitary products in the blood stream does not declare that such products are not normally liberated from the secreting pituitary cells—and therefore not true hormones—the short list of hormones that have been so recovered deserves mention.

Prolactin has been reported in post-partum human serum by Tesauro (13); our laboratory has detected it in the serum of pregnant mares, and Leblond (14) found it also in the serum of lactating mares. Geschickter and Lewis (15) found notable quantities of prolactin in cystic human mammaries and in the mammaries of post-partum cows. Leblond and Noble (16) find traces in whole fish liver and brain, and Bates and Riddle (unpublished) confirmed this result with pigeon liver. Part, but not all, of these results were obtained by the extraordinarily sensitive *local* crop-sac test of Lyons and Page (17); it is doubtful whether a test equally as sensitive as this latter test is now available for any other anterior pituitary product. Moreover, the implantation of intact untreated pituitaries of pigeons (Riddle and Schooley, 18), of fowl (Burrows and Byerly, 19) and of rats (Reece and Turner, 20) has permitted the detection of prolactin in all these untreated glands.

Follicle-stimulating hormone (FSH) is well known to be present in large quantities in the serum of mares during most of

the term of pregnancy (Cole and Hart, 21). Many studies have indicated the presence of this hormone in human blood during pregnancy, and after castration or the menopause. Again, the implantation of intact untreated pituitaries of mice and rats—in the classic experiments of Smith and Engle (22) and Zondek and Aschheim (23)—supplied the original evidence that this hormone exists in the pituitary.

Luteinizing hormone (LH) extracted from urine and placenta seems to differ from that of pituitary origin. Hellbaum (24) reports the isolation from mare serum of an LH which is similar to pituitary LH. Again, the implantation of untreated pituitaries produced luteinization (22, 23)—though this alone does not establish the existence of a luteinizing hormone of pituitary origin.

Thyrotropic hormone apparently has not been satisfactorily demonstrated in the blood—probably because a sufficiently delicate test for minute amounts of it have not yet been developed. A few cc. of mare serum—very rich in FSH—were found incapable of affecting the metabolic rate of doves (2). But implantation of surviving anterior lobe to the vicinity of the thyroid has supplied evidence of the capacity of such tissue to stimulate the thyroids (Atwell, 25; Etkin, 26).

Other alleged pituitary hormones can not here be given a similar individual survey. But we note our opinion that evidence of the types (and in the volume) so easily cited for prolactin and FSH is not available for the several alleged entities: growth, adrenotropic, diabetogenic, ketogenic, fat metabolism, antagonist, interstitial cell stimulating, pancreatropic and parathyrotropic. It is true of course that less sensitive tests may have interfered with positive findings in these cases. The growth response in rats has indeed been obtained from untreated rat (and pig) pituitary implants (Smith, 27; Smith and Dortzbach, 28); but on the point here in question that result is quite indecisive since other data suggest that the growth response rests upon the sum of helpful things contributed by more than one pituitary hormone. Smith (27) was the first to show that the thyroid hormone (desiccated thyroid), added to "growth" hormone, could cause more rapid growth (hypophysectomized rats) than did the growth extract alone.

Some at least of the above list of "alleged entities" almost certainly rest upon the wholly unsubstantial basis that the injection of a pituitary extract was followed by a particular

response, this response thereafter gratuitously supplying a name for an imagined product in the pituitary—whereas the response may in fact rest upon (a) a hormone produced in any such organ as the thryoid, gonad, adrenal, pancreas, liver, or indeed (b) upon a combined action of hormones produced in several of these organs; or, again (c), some responses thus translated into entities may rest, in part at least, upon the contamination of true anterior lobe hormone by effective amounts of intermedin or posterior lobe hormones. Few things are easier than to find a hitherto unrecognized response to the administration of mixed pituitary extracts; and few things are more difficult than to prove that the new response is produced by a hitherto unrecognized specific anterior pituitary product.

It is against the background of the preceding discussion that, for the present, it seems helpful and possible to think of two groups of substances elaborated by the pituitary; and also possible to associate the one group with the eosinophils and the other with the basophils. Since cytological phenomena within both these types of cells show waxing and waning aspects of the process of hormone formation (secretion) it seems possible that the effective molecules formed while the cell is being forced to halt secretion is not the exact equivalent of that formed under conditions which accelerate its secretory activity (thus recalling the production successively of estrone and progesterone by the same ovarian cell—or from a derivative of it). Though this concept has no experimental basis it would permit us to rationalize the production of more than one (chemically related) hormone in the same cell or type of cell. A gonadotropic chemical relative(s) of FSH, or even thyrotropic hormone, might thus arise from the basophil; again, perhaps prolactin-adrenotropin and thyrotropic might come from reverse phases of the functioning of individual eosinophil cells—some of which are in regressive phase at the moment others are highly active.

We here recall that though one is forced to speculate there should be an end to it. It is now an observed fact that an element (light) of the external environment (Rowan, 29) and the nervous system (Friedgood and Pincus, 30; Haterius and Derbyshire, 31) both share in regulating the output of at least some pituitary hormones (FSH). To this must be added important facts indicating that the production of certain pituitary hormones is affected by the output of other pituitary hormones or by secondary products of the action of a pituitary hormone. Thus a

release of gonad-stimulating hormone leads to a stimulation of sex-hormones (estrone, testosterone) and these usually so act upon pituitary cells as to check or suppress the further release of FSH (Moore and Price, 32; and others), while the estrone induces a release of LH (Hohlweg, 33; Fevold, Hisaw and Greep, 34). Again, it is reported (Bates, Riddle and Lahr, 35) that prolactin (an eosinophilic product) is capable of suppressing the release of FSH (a basophilic product) in mature birds. These few instances of means of control of pituitary hormone output have wide biological significance since they permit us to begin to see the regulatory mechanism for some of the most intricate aspects of biologic organization and adaptation.

SOME RESPONSES TO SPECIFIC HORMONES

We may now consider briefly certain results recently obtained in our own laboratory which have bearing upon some of the general views already discussed. We first examine some results dealing with relationships of the prolactin-adrenotropin component (of eosinophilic origin) to carbohydrate and fat metabolism and to growth.

Data of Riddle and Dotti (36; and unpublished) show that in pigeons, doves and rabbits (apparently not in rats) the *blood sugar* is increased by injecting these animals with prolactin. Table I gives some typical findings on pigeons.

Most of the preparations used in these studies were in fact called prolactin; but certainly some of those preparations (not Nos. 380, 394H) had power to enlarge the adrenals of 21-day old rats or partially to repair the adrenal cortex of hypophysectomized pigeons. These cortical responses have been assigned to a separate substance—corticotropin—by Collip, Anderson and Thomson (37), Anselmino, Hoffman and Herold (38), Lyons (39) and Moon (40). At the moment we can exclude corticotropin or "adrenotropin" as a causative agent for the tabulated changes in blood sugar, though its presence does affect glycogen storage as noted below. We can also exclude such substances as intermedin, posterior lobe hormones, FSH, LH and thyrotropic hormone as the effective agents. Many of the effective preparations were first subjected to heat (boiling for 1 hour, or 60° C. for 5 hours).

Other data (Johnson and Riddle, unpublished) show that some of these same prolactin preparations also markedly increased the amount of histologically demonstrable *glycogen* in

TABLE I

Excerpt from data of Riddle and Dotti. Action of prolactin (3 tests of adrenotropin at bottom) on blood sugar in pigeons fasted 20–24 hours.

Preparation	Operative Procedures Used	Since Last Injection	No. Tested	Dosage		Glucose Found	
				Daily	Term	Control	Test
		hrs.		units prolac.	days	mgm.	mgm.
Prolactin, #380	Normals	24	8	30	1	192	241
" "	"	24	8	30	2	192	245
" "	"	24	8	30	3	192	256
Prolactin, #495H	Hypct.-castrate	24	3	18	8	183	211
" "	Hypophysectomy	24	2	18	8	188	214
" "	Hypct.-castrate	24	1	18	8	178	225
" "	Thyroidectomy	24	3	18	8	197	226
" "	Partial thydct	24	2	18	8	189	212
" "	Hypophysectomy	25	3	18	4	187	207
" "	Hypophysectomy	24	2	30	7	178	219
" "	Partial adrect	18	7	30	4	194	208
" "	Pt. adrect.-castr	18	2	30	4	179	225
" "	Pt. adrect.-thydct	18	1	30	4	192	221
" "	Pt. adrect.-hypct	18	2	30	4	185	219
Adrenotropic* #505	Thyroidectomy	21	3	1 (10 mg.)	4	219	232
" "	Hypophysectomy	21	1	1 (10 mg.)	4	167	165
Prolactin, #394H	Hypophysectomy	21	3	24	4	178	214
Adrenotropic* # 576	Hyp.-pancreatectomy	4–27	2	10 (10 mg.)	1–2	229	281
Prolactin #394H	Hyp.-pancreatectomy	4–27	4	80	1–2	223	275

*As prepared by method of Lyons (39) and Moon (40) by Dr. R. W. Bates; 10 mgm. daily in all tests, and containing the amount of prolactin indicated.

For performing, and checking the completeness of the various operations on animals utilized here, we are indebted to Dr. J. P. Schooley of our laboratory.

the livers of normal and hypophysectomized birds. This response followed the use of prolactin preparations with which we could demonstrate no enlargement of the 21-day rat adrenal, though it was evidently more pronounced when preparations having capacity to enlarge such adrenals were used. This result, however, was not further increased by the use of all the hormones contained in a whole extract of the pituitary. It seems that both prolactin and adrenotropin share in one phase of carbohydrate mobilization and utilization; other available evidence (41) points to rapid enlargement of livers (also intestine and pancreas) as a true prolactin response.

Still other data (Johnson and Riddle, unpublished) clearly indicate that prolactin (adrenotropic?) also increases the *fat* content of these bird livers (which are simultaneously both enlarging and increasing their glycogen content). This increase of liver fat (in hypophysectomized pigeons) can apparently be somewhat emphasized by the adrenotropin element of whole pituitary extracts. Possibly bearing on this point is the observation that, in normal doves, the injection of *estrone* increases the amount of fat in the liver. This ovarian hormone had no apparent effect upon hepatic glycogen.

From the above one gets indications that responses traceable to the prolactin-adrenotropin complex—at one point (liver fat) associated with action of a secondary product of the FSH complex—may encompass or include responses attributed to such additional "entities" as diabetogenic, ketogenic, and fat metabolism (and pancreatropic?).

Further consideration of prolactin, or possibly of the prolactin-adrenotropin complex, will indicate that in pigeons it too is responsible for splanchnomegaly—hitherto considered an aspect of the growth response and ascribable to a "growth" hormone. The data of Table 2 show that body growth, with rapid and excessive increase of liver weight, is obtained in Carneau pigeons by the administration of relatively highly purified preparations of prolactin. At three weeks after hatching the rapidly growing young pigeon shows crop-gland stimulation from prolactin produced in its own pituitary; and at this stage it shows—in addition to an amazing rate of body growth—relative *overgrowth* in liver, intestines, and probably in the pancreas. When similar birds were somewhat older, and in growth stasis, the administration of prolactin was followed by a resumption of body growth and by overgrowth of liver and

TABLE II

Excerpt from data of Bates, Riddle, Lahr and Schooley (41). Aspects of splanchnomegaly associated with the phase of rapid growth (1.3 months) in uninjected young White Carneau Pigeons and in similar young (2.2 mo.) injected for four days with prolactin. The standard deviation of the mean is given with each averaged value.

Route of Injection	No. of Birds	Age	Daily Dose	Body Weight	Liver	Intestine		Thyroids	Crop-glands
						Length (Gizzard to Anus)	Empty Weight		
		mo.	mgm.	grams	grams	cm.	grams	mgm.	mgm.
	Uninjected; young gest (1.3 mo.) group in extremely rapid growth.								
	12	1.3	.....	298± 4.9	9.3±0.3	117.8±2.2	10.3±0.4	30.5±1.7	1670± 70
	15	1.5	.....	457±11.6	10.0±0.3	117.8±1.4	13.2±0.4	33.3±1.5	1490± 49
	36	1.5	.....	431± 5.4	9.8±0.3	115.9±1.7	10.5±0.2	32.4±1.0	1630± 53
	27	2.2	.....	461±10.7	10.7±0.4	110.8±2.0	12.0±0.3	41.1±3.1	1245± 33
	Injected with iso-soluble fraction No. 474=FSH+ thyrotropic.								
Two routes*.....	10	2.2	5	453-35[1]	8.4±0.6	102.3±3.4	.....	77.7±12.0	1150± 64
	Injected with iso-insoluble fraction No. 469=prolactin.								
Intravenous.....	10	2.2	1	498+15	10.7±0.5	113.1±3.4	.....	42.7±2.4	1610±113
Intramuscular.....	15	2.2	1	457+24	10.8±0.6	111.1±2.9	.....	40.6±1.8	2355±188
Intracutaneous.....	10	2.2	1	460+43	13.3"0.9	117.3±4.6	.....	40.5±1.8	3790±233
Subcutaneous.....	10	2.2	0.1	466+ 5	9.3±0.7	104.4±1.9	.....	33.1±2.0	1255± 59
"	15	2.2	1	459+47	12.6±0.6	125.4±4.1	15.3±0.8	37.4±2.5	3940±232
"	10	2.2	5	453+75	16.4±0.9	127.0±4.4	.....	42.0±3.6	5845±476

*Intramuscular (5) and subcutaneous (5).
[1]Gain or loss of weight is indicated for all injected birds.

intestines (still other data obtained with Drs. Schooley, Lahr and Bates show this for the pancreas, and show that these aspects of body growth and visceral overgrowth are likewise obtained in hypophysectomized pigeons). Administration of an isosoluble pituitary preparation, known to be rich in FSH and thyrotropic hormones and probably containing all anterior lobe hormones except prolactin, produced none of these effects.

Though the above-described splanchnomegaly has not been induced in the rat, by the same preparations of prolactin which

TABLE III

Excerpt from data of Riddle and Dotti. Effect of *cortin* (Kendall) on blood sugar of doves and pigeons fasted 20–24 hours.

Animal Used (Operations Indicated)	Since Last Injection	No. Tests	Dosage		Glucose of Blood per 100 cc.	
			Daily	Term	Control	Test
	hrs.		cc.	days	mg.	mg.
Normal doves	7	12	0.3*	3–9	205	244
Normal doves	6[1]	4	0.5*	1	208	226
Normal doves	6[1]	4	0.5*	1	208	205[2]
Hypct. pigeons	6[1]	7	1.0*	1	173	193
Hypct. pigeons	6[1]	7	1.0*	1	173	175[2]
Thydct. pigeons	23	2	0.5	3–10	210	203
Part. thydct. pigeons	23	4	0.5	3–10	203	203
Thydct. pigeons	7[1]	3	1.0[1]	4	207	255
Part. thydct. pigeons	7[1]	2	1.0[1]	4	196	236
Hypct. pigeons	23	2	0.5	3–8	205	201

*Dose divided (twice daily).
[1]Intraperitoneal injection.
[2]Cortin inactivated by heat (96° C., 2 hrs.) used here.

produce it in doves and pigeons, positive results are regularly obtained in these latter species. The allocation to prolactin (or to heated prolactin-adrenotropin preparations) of these aspects of growth and overgrowth in these species provides a basis for further doubt as to the separateness or singleness of a "growth" hormone in the pituitary.

Returning now to the rôle of the adrenal cortex in carbohydrate metabolism one first notes that Long and Lukens (see Long, 42) have shown that glycosuria is produced in cats and rats by the effective pituitary hormone (or hormones) in the absence of both the pancreas and the hypophysis, but not in the absence of the adrenals. They further found that samples of

TABLE IV

Excerpt from data of Riddle and Dotti. Effect of pituitary (top) and of sex hormones (below) on serum calcium.

Preparation of Hormone	Dosage		Animals Used		Serum Calcium (mgm. per 100 cc.)	
	Quantity Daily	Term	No.	Kind	Control	Test
	cc. or units	days			mg.	mg.
Whole A. P. extr. (all A. P. hormones)	0.3 cc.	3	6	♂ ♀ Hypct. juv. pigeons	9.8	11.1
Prolactin	15.0 d. u.	10	10	♂ ♀ Hypct. juv. pigeons	9.8	9.9
FSH (+LH?) Mare serum	0.4 cc.	9	13	♂ ♀ Hyp. adult pigeons	9.3	10.8
FSH (+LH?) Mare serum	1.0 cc.	6	2	♀ Partial. adrenalect., ad.	11.6	17.0
FSH+thyrotropic (from A. P.)	2 mg.	5	2	♀ Thyroidectomy, ad	10.2	20.2
Estrone	250 R. U.	6	7	♂ ♀ Normal juv. pigeons	10.1	19.3
"	200 R. U.	7	2	♂ Hypct. pigeons, ad	9.0	25.1
"	3000 R. U.	2	2	♀ Dogs	10.0	12.3
"	3000 R. U.	8	3	♀ Rabbits	12.6	13.1
Dihydroestrone	1000 R. U.	3	3	♀ Non-laying hens	12.3	22.1
"	200 R. U.	6	2	♂ Part. hypct. ad. pigeons	9.4	10.7
"	375 R. U.	7	3	♂ ♀ Castrate rats	10.1	10.9
Progesterone	1 Rb. U.	3	2	♂ Normal pigeon, ad	10.2	12.0
"	0.1 Rb. U.	10	2	♀ Normal rats	10.4	11.6
Testosterone	2.5 mgm.	7	2	♂ Hypct. pigeon, ad	9.0	8.6
"	2.0 mgm.	7	4	♂ ♀ Normal pigeons, ad	10.1	9.9
"	5.0 mgm.	3	3	♂ ♀ Rabbits	13.1	13.1
Androstendiol	3.5 C. U.	7	2	♂ ♀ Hypct. pigeons, ad	9.3	9.3

prolactin (probably with some adrenal-stimulating power) prepared in our laboratory and also adrenotropin (probably containing prolactin) prepared by Collip were both very effective in the production of glycosuria in animals with intact adrenals. Houssay and Leloir (43), however, do not regard the adrenals as necessary to this response in toads and dogs. Britton (44) has long maintained that cortin (adrenal cortical hormone) raises the blood sugar of the mammalian species studied by him. The data cited below support Britton's views and extend the observations to birds.

In Table 3 are given some data of Riddle and Dotti (36, and unpublished) showing that in doves and pigeons cortin increases the blood sugar during the first several hours after injection but that this effect disappears within less than 23 hours. Of course the pituitary hormone which stimulates the cortex would provide for a continuous secretion of cortin and thus for its continuity of action on the blood sugar. We are much indebted to Dr. E. C. Kendall, Mayo Clinic, for the cortin used in the tabulated tests. Cortin kindly supplied by Dr. David Klein, The Wilson Laboratories, and Dr. R. L. Zwemer, Columbia University, gave similar results.

These several items indicate that the diabetogenic response is, in part at least, mediated through other incretory glands, and that cortin possibly shares in this response. Cortin—as shown by the work of Hartman, of this University, and by others—contributes so much to the well-being of the organism that it is difficult to conceive its exclusion from the growth response, and particularly to that response in hypophysectomized animals. Again, Hitchcock and Grubbs (45) recently report that the administration of cortical extract to normal human beings tends to increase their muscular efficiency during light work; and this sparing of heat production may have significance in the growth process. Finally, it is not improbable that the adrenal cortex produces still other hormones than cortin, and that hitherto their effects may have helped to swell the number of products supposedly produced in the pituitary gland.

We conclude this discussion with a very brief consideration of a response obtained with an FSH component (of basophilic origin), and with the secondary products (sex hormones) of its action on the gonads. Originally this study was directed to an examination of the evidence for the production by the anterior pituitary of a special "parathyrotropic" hormone—a

hormone alleged to stimulate the parathyroid glands to an increased production of parathormone, which in turn is known to increase the blood calcium.

In this study (Riddle and Dotti, 46; and unpublished data) it was soon found that prolactin and cortin were without effect, but the injection (prolonged and adequate dosage) of the FSH component into suitable animals resulted in increased amounts of calcium in the blood serum. Whole pituitary extracts gave a like result. The serum from pregnant mares, with FSH as the sole probably active factor, is effective. Later it was found that the *female sex hormones* have this power, and that male sex hormones have little or no similar action. Typical results are given in Table 4. We are greatly indebted to Dr. Erwin Schwenk, of the Schering Corporation, for the sex hormones used in that study.

Though it is uncertain whether or to what extent the parathyroids share in the response (castration prevents it) to FSH it is evident that the calcium elevating property of the sex hormones is exercised in the absence of either hypophysis, gonads, thyroids, and probably the parathyroids. It is also evident that before one can accept "parathyrotropic" pituitary hormone as an entity these new facts concerning the rôle of FSH and sex hormone must be concurrently examined.

On this day of continuous flux—along with gratifying advance—in all that pertains to the hormones of the anterior pituitary one may be neither too positive nor profitably attempt to be encyclopedic. In the present effort we have ventured—and have exposed all flanks in stating a point of view which we hope may be of momentary service. A little, but much too little, of the documentation of new research has indicated a part of the basis for an opinion that few true anterior pituitary hormones exist; that a greater variety of unfinished pituitary products exist; that secondary products of pituitary hormone action in other glands may have been mistaken for primary pituitary products; and that the true anterior pituitary hormones perhaps arrange themselves in two groups.

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